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09/648,389	08/25/2000	David Pinsky	62683/JPW/JML	5890

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Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036

EXAMINER

GIBBS, TERRA C

ART UNIT	PAPER NUMBER
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1635

17

DATE MAILED: 08/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/648,389

Applicant(s)

PINSKY ET AL.

Examiner

Terra C. Gibbs

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 July 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 16 and 18-36 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 16 and 18-36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 15, 2003 has been entered.

Claims 1, 3, 5, 7, 9-15 and 17 have been canceled. Claims 16, 18, 19, 25, and 27 have been amended. New claims 28-36 are acknowledged.

Claims 16, and 18-36 have been examined on the merits.

Response to Arguments

Applicants Amendment and Response filed April 15, 2003 in Paper No. 13, has been considered. Rejections and/or objections not reiterated from the previous office action mailed January 9, 2003 in Paper No. 12 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Election/Restrictions

Peptide, peptidomimetic, small molecule, organic molecule, inorganic molecule, and antibody compound inhibitors which inhibit the expression of Egr-1 are withdrawn from further

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consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement filed March 28, 2002 in Paper No. 9.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16, 27, 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16 and 27 are indefinite because they recite the limitation "vascular tissue". There is insufficient antecedent basis for this limitation in the claim because the claims earlier recite "ischemic tissue". Appropriate correction is required.

Claim 31 is indefinite because it recites the term "fragment thereof". The term "fragment thereof" follows a peptide, a peptidomimetic compound, a nucleic acid molecule, a small molecule, an organic compound, an inorganic compound, or an antibody. First, it is unclear how "a fragment thereof" applies to a peptidomimetic compound, an organic compound, or an inorganic compound. Second, it is unclear whether the "fragment thereof" is a fragment of a peptide, a nucleic acid molecule, a small molecule, or an antibody. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16 and 18-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for reducing ischemic damage to a tissue being transplanted into a subject comprising contacting the tissue with SEQ ID NO: 1 *ex vivo*, does not reasonably provide enablement for a method for reducing ischemic damage to tissue being transplanted into a subject comprising contacting the tissue with any inhibitor of Egr-1 *ex vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 16 and 18-36 are drawn to a method for reducing vascular injury during reperfusion of an ischemic tissue comprising contacting the tissue with a nucleic acid comprising a polynucleotide sequence complementary to Egr-1, before, during or after reperfusion.

The instant invention specification provides general methodologies for decreasing Egr-1 mRNA and protein expression in rat lungs preserved with Egr-1 antisense (SEQ ID NO: 1) *ex vivo* (see Figures 10 and 11). Additionally, the instant specification shows arterial oxygenation (gas exchange) and survival times of rats transplanted with preserved lungs treated with Egr-1 antisense (SEQ ID NO: 1) *ex vivo* (see Figures 12 and 13).

The unpredictability of the art of antisense therapy in general further adds to the lack of enablement for the current invention. For example, Branch (TIBS Vol. 23, February 1998)

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addresses the unpredictability and the problems faced in the antisense art with the following statements: “Antisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. However, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven.”; “To minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. This is a challenging quest.”; “However, their unpredictability confounds research application of nucleic acid reagents.”; “Non-antisense effects are not the only impediments to rational antisense drug design. The internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules.”; “Years of investigation can be required to figure out what an ‘antisense’ molecule is actually doing,...”; “Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters.”; “Because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. Antisense compounds are no exception. As is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range.”; “Because it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells.”; “Binding is the rare exception rather than the rule, and antisense molecules are excluded from

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most complementary sites. Since accessibility cannot be predicted, rational design of antisense molecules is not possible.”; and, “The relationship between accessibility to oligonucleotide (ODN) binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored...It is not yet clear whether *in vitro* screening techniques...will identify ODN's that are effective *in vivo*.”

Jen et al. (Stem Cells, 2000, Vol. 18:307-319) discuss antisense-based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al. discuss the advances made in the art but also indicate that more progress needs to be made in the art. In the conclusion of their review, Jen et al. assert, “Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive.” It is also stated “The key challenges to this field have been outlined above. It is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. A large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy.” It is clear from Jen et al. that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

Additionally, in a published review of the potential use of antisense oligonucleotides as therapeutic agents, Gewirtz et al. (Proc. Natl. Acad. Sci, 1996 Vol. 93:3161-3163) teach that the inhibitory activity of an oligonucleotide depends unpredictably on both the sequence and structure of the nucleic acid target site and the ability of the oligonucleotide to reach its target (page 3161, second and third columns). Gewirtz et al. conclude by observing that, “the antisense

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approach has generated controversy with regard to mechanism of action, reliability, and ultimate therapeutic utility" and "that efforts should be increased...to learn how they may be used successfully in the clinic" (page 3162, middle column, last paragraph). Furthermore, although applicants give evidence of the Egr-1 inhibitory activity of SEQ ID NO: 1 in cells in culture and *ex vivo*, such evidence is not a representative number of species of the claimed genus of Egr-1 inhibitors (see 112, first paragraph rejection below for lack of written description).

As per the section 112, first paragraph, for lack of written description rejection (see page 10 below), applicants are not in possession of any inhibitor of Egr-1 as claimed, other than SEQ ID NO: 1. The specification does not adequately describe the structures and physical properties of all inhibitors of Egr-1. Given its broadest reasonable interpretation, the claims encompass nucleic acids where the specification does not provide sufficient description that would allow one of skill in the art to predict the structures of all nucleic acids that inhibit the expression of Egr-1, isolated from other sources, including all polymorphic, allelic and splice variants of this mRNA. Thus, it would require undue experimentation to determine what inhibitors would act to inhibit Egr-1 expression since one of skill in the art would have to engage in undue trial and error experimentation to design inhibitors that would inhibit Egr-1 expression without the requisite knowledge of primary structures of inhibitory compounds or mechanisms of action. The quantity of experimentation required to practice the invention as claimed would involve the designing of oligonucleotides that would inhibit Egr-1, for example. Without specific guidance from the specification, the skilled artisan is left to guess what oligonucleotides possess such activity and to further guess what sequences would elicit an inhibitory response to Egr-1 since it

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cannot be determined from the specification through what mechanism the oligonucleotides would exert its inhibitory activity, i.e., antisense, triplex, aptamer, or unknown mechanisms.

In view of the unpredictability in the art, the specification as filed does not provide adequate guidance or examples that would show by correlation how one skilled in the art would practice the claimed invention commensurate in scope with these claims without having to engage in trial and error or undue experimentation. The specification as filed contemplates an *in vivo* method for reducing vascular injury during reperfusion of an ischemic tissue comprising contacting the tissue with a nucleic acid comprising a polynucleotide sequence complementary to Egr-1. However, the instant specification does not show any specific link between decreasing Egr-1 mRNA and protein expression and increasing survival times, and arterial oxygenation in rat lungs preserved with Egr-1 antisense (SEQ ID NO: 1) *ex vivo* such that an *in vivo* method for reducing vascular injury during reperfusion of an ischemic tissue comprising contacting the tissue with a nucleic acid comprising a polynucleotide sequence complementary to Egr-1 would be an apparent option. It is unclear how the specific *ex vivo* data is correlated with/or representative of an *in vivo* method for reducing vascular injury during reperfusion of an ischemic tissue comprising contacting the tissue with a nucleic acid comprising a polynucleotide sequence complementary to Egr-1, with any polynucleotide sequence complementary to Egr-1. It is also unclear how any polynucleotide sequence complementary to Egr-1 will reduce vascular injury during reperfusion of an ischemic tissue *in vivo* where no specific guidance (i.e. specific mode of treatment, delivery route, tissue specificity, etc.) is provided.

The specification does not provide particular guidance or particular direction for an *in vivo* method for reducing vascular injury during reperfusion of an ischemic tissue comprising

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contacting the tissue with a nucleic acid comprising a polynucleotide sequence complementary to Egr-1. The specification does not provide guidance for the delivery of antisense compounds into the target organ and target cells *in vivo* in quantity sufficient to inhibit Egr-1 expression. While the specification provides guidance to addressing antisense compound administration to cells and pulmonary grafts *in vitro* and *ex vivo*, the specification provides no particular nexus between an *in vivo* method for reducing vascular injury during reperfusion of an ischemic tissue comprising contacting the tissue with a nucleic acid comprising a polynucleotide sequence complementary to Egr-1, as contemplated by the specification. The specification provides no particular guidance of direction for addressing the problems of targeting, permanence and quantity of expression of the gene in question, immunogenicity, etc, for nucleic acid/antisense targeting Egr-1 *in vivo*. The specification provides no particular guidance or direction for reducing vascular injury during reperfusion of an ischemic tissue using a polynucleotide sequence complementary to Egr-1 of the claimed invention.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use the claimed invention commensurate in scope with these claims. Due to the lack of specific guidance in the specification as filed and the lack of correlation between decreasing Egr-1 mRNA and protein expression and increasing survival times, and arterial oxygenation in rat lungs preserved with Egr-1 antisense (SEQ ID NO: 1) *ex vivo*, and an *in vivo* method for reducing vascular injury during reperfusion of an ischemic tissue comprising contacting the tissue with a nucleic acid comprising a polynucleotide sequence complementary to Egr-1, one of

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skill in the art would require specific guidance to practice the current invention. The current specification does not provide such guidance to target and inhibit the expression of Egr-1 *in vivo* and one of skill in the art would be required to perform trial and error or undue experimentation. The quantity of experimentation required to practice the invention would include the de novo determination of how to engineer and deliver an antisense targeting Egr-1 such that vascular injury during reperfusion of an ischemic tissue would be reduced to any degree, particularly, in view of the obstacles needed to overcome to use antisense therapies as exemplified in the references discussed above.

Claims 16, 18-25, 27, and 28-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is for lack of written description.

The instant claims read on a method for reducing vascular injury during reperfusion of an ischemic tissue comprising contacting the tissue with a compound which inhibits Egr-1 expression, wherein the compound is a nucleic acid molecule or a fragment thereof.

The claimed invention encompasses nucleic acid compounds that inhibits all forms of the Egr-1 gene, which includes sequences from other species, mutated sequences, polymorphic and allelic variants, splice variants, sequences that have an unspecified degree of identity (similarity, homology), and so forth. The specification as filed provides only a description of a polynucleotide sequence complementary to Egr-1 (see SEQ ID NO: 1, for example).

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The specification provides only a description of a polynucleotide sequence complementary to Egr-1 (see SEQ ID NO: 1, for example), wherein such polynucleotide sequence complementary to Egr-1 is effective to inhibit expression of the target sequence. However, the specification as filed, does not provide sufficient description that would allow one of skill in the art to use SEQ ID NO. 1 to predict the structures of all nucleic acid compounds that inhibit the expression of Egr-1, isolated from other sources, including all polymorphic, allelic and splice variants of this mRNA.

The specification fails to describe the complete structure of a representative number of species of the claimed genus. See the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement (Vol. 66, No. 4, pages 1099-1111). These guidelines state that: "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention." In the instant case, the specification does not describe or identify characteristics that can be used to distinguish species of the claimed genus.

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Additionally, “[T]he skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.”

Applicant's specification does not provide a sufficient number of representative species of nucleic acid molecules that inhibit the expression of Egr-1, which would allow one of skill in the art to predict the structures of all members of the claimed genus of compounds. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Therefore, the specification does not describe the claimed compounds in such full and concise terms so as to indicate that the applicant had possession of these compounds at the time of filing of this application. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.).

Conclusion

No claims are allowable.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-8693 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
August 6, 2003


KAREN LACOURCIERE
PATENT EXAMINER